10/03/03
Allowed

(SEQ ID NO:26), A2 (SEQ ID NO:27)), B (B1 (SEQ ID NO:31), B2 (SEQ ID NO:32), C (C1 (SEQ ID NO:33), C2 (SEQ ID NO:34)), D (SEQ ID NO:37), E (SEQ ID NO:40)) and loops (AB1 (SEQ ID NO:28), AB2 (SEQ ID NO:29), AB3 (SEQ ID NO:30), CD1 (SEQ ID NO:35), CD2 (SEQ ID NO:36), DE1 (SEQ ID NO:38), DE2 (SEQ ID NO:39)) of interferon-beta-1a (SEQ ID NO: 25). See Example 1.--

Please replace the pending sequence listing with the enclosed sequence listing.

In the claims:

Please cancel claims 25-40 without prejudice or disclaimer as drawn to a non-elected invention. Please amend claims 1, 5, 7-8, 15, 19 and 22, cancel claims 3-4, 9-10, 14, 16, 17 and 21, add new claims 41-48 and replace the pending claims with the following claims:

1. (Amended) A composition comprising ~~the~~ glycosylated interferon-beta-1a ~~of~~ SEQ ID NO: 25 coupled to a non-naturally-occurring polymer at an N-terminal end of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety.

2. The composition of claim 1, wherein the polyalkylene moiety is coupled to the interferon -beta by way of a group selected from an aldehyde group, a malcimide group, a vinylsulfone group, a haloacetate group, plurality of histidine residues, a hydrazine group and an aminothiol group.

3. (Amended) The composition of claim 1, wherein the interferon -beta-1a of SEQ ID NO: 25 is an interferon -beta-1a fusion protein.

4. The composition of claim 3, wherein the interferon -beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

7. (Amended) A composition comprising ~~the~~ glycosylated interferon-beta-1a ~~of~~ SEQ ID NO: 26 coupled to a non-naturally-occurring polymer at the N-terminus of said glycosylated interferon-

beta-1a, said polymer comprising a polyalkylene glycol moiety.

8. (Amended) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 coupled to a polymer comprising a polyalkylene glycol moiety, wherein the interferon -beta- 1a is coupled to the polymer at a site on the interferon-beta-1a that is an N- terminal end, wherein the physiologically active interferon -beta 1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon -beta composition has an activity at least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by an antiviral assay.

11. The composition of claim 8, wherein the interferon -beta-1a is coupled to the polymer at a site by way of a glycan moiety of the interferon -beta-1a.

12. The composition of claim 8, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

13. The composition of claim 12, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

15. (Amended) A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 N-terminally coupled to a polymer comprising a polyalkylene glycol moiety, wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

18. The composition of claim 15, wherein the interferon -beta is coupled to the polymer at a site by way of a glycan moiety on the interferon-beta.

9 7
19. (Amended) The composition of claim 15, wherein the interferon-beta-1a is an interferon beta fusion protein.

10 9
20. The composition of claim 19, wherein the interferon beta fusion protein comprises a portion of an immunoglobulin molecule.

11
22. (Amended) A stable, aqueously soluble, conjugated interferon-beta-1a complex comprising a interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25, N-terminally coupled to a polyethylene glycol moiety, wherein the interferon-beta-1a is coupled to the polyethylene glycol moiety by a labile bond, wherein the labile bond is cleavable by biochemical hydrolysis and/or protcolysis.

5 7 11
23. A interferon-beta composition according to claims 1, 15 or 22, wherein the polymer has a molecular weight of from about 5 to about 40 kilodaltons.

6 5
24. A pharmaceutical composition comprising the interferon-beta composition of claim 23.

20 15 comprising the amino acid sequence set forth in
41. (New) The composition of claim 37, wherein the glycosylated interferon-beta-1a of SEQ ID NO: 26 is an interferon-beta-1a fusion protein.

21 20
42. (New) The composition of claim 41, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

22
43. (New) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO:26, coupled to a non- naturally-occurring polymer at the N-terminus of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has an activity at

least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by an antiviral assay.

23 ~~44~~. (New) The composition of claim ~~43~~ 22, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

24 ~~45~~. (New) The composition of claim ~~44~~ 23, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

12 ~~46~~. (New) A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a, comprising the amino acid sequence of SEQ ID NO: 25, N-terminally coupled to a polymer comprising a polyalkylene glycol moiety, wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

13 ~~47~~. (New) The composition of claim ~~46~~ 12, wherein the interferon-beta-1a is an interferon beta fusion protein.

14 ~~48~~. (New) The composition of claim ~~47~~ 13, wherein the interferon beta fusion protein comprises a portion of an immunoglobulin molecule.

12/19/03 Was not considered

In the claims:

Please amend claims 12 and 43 as follows:

1. (Previously presented) A composition comprising a glycosylated interferon-beta-1a comprising the amino acid sequence set forth in SEQ ID NO: 25 coupled to a non-naturally-occurring polymer at an N-terminal end of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety.

2. (Previously presented) The composition of claim 1, wherein the polyalkylene moiety is coupled to the interferon-beta by way of a group selected from an aldehyde group, a maleimide group, a vinylsulfone group, a haloacetate group, plurality of histidine residues, a hydrazine group and an aminothiol group.

3. (Cancelled).

4. (Cancelled).

5. (Previously presented) The composition of claim 1, wherein the interferon-beta-1a of SEQ ID NO: 25 is an interferon -beta-1a fusion protein.

6. (Previously presented) The composition of claim 5, wherein the interferon -beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

7. (Previously presented) A composition comprising a glycosylated interferon-beta-1a comprising the amino acid sequence set forth in SEQ ID NO: 26 coupled to a non-naturally-occurring polymer at the N-terminus of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety.

8. (Previously presented) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25, coupled to a polymer comprising a polyalkylene glycol moiety, wherein the interferon -beta-1a is coupled to the polymer at a site on the interferon-beta-1a that is an N- terminal end, wherein the physiologically active interferon -beta 1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon -beta composition has an activity at least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by an antiviral assay.

9. (Cancelled).

10. (Cancelled).

11. (Previously presented) The composition of claim 8, wherein the interferon-beta-1a is coupled to the polymer at a site by way of a glycan moiety of the interferon-beta-1a.

12. (Previously presented) The composition of claim 8, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

13. (Previously presented) The composition of claim 12, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

14. (Cancelled).

15. (Previously presented) A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25 N-terminally coupled to a polymer comprising a polyalkylene glycol moiety, wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta 1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

16. (Cancelled).

17. (Cancelled).

18. (Previously presented) The composition of claim 15, wherein the interferon-beta is coupled to the polymer at a site by way of a glycan moiety on the interferon-beta.

19. (Previously presented) The composition of claim 15, wherein the interferon-beta-1a is an interferon beta fusion protein.

20. (Previously presented) The composition of claim 19, wherein the interferon beta fusion protein comprises a portion of an immunoglobulin molecule.

21. (Cancelled).

22. (Previously presented) A stable, aqueously soluble, conjugated interferon-beta-1a complex comprising a interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 25, N-terminally coupled to a polyethylene glycol moiety, wherein the interferon-beta-1a is coupled to the polyethylene glycol moiety by a labile bond, wherein the labile bond is cleavable by biochemical hydrolysis and/or protcolysis.

23. (Previously presented) A interferon-beta composition according to claims 1, 15 and 22, wherein the polymer has a molecular weight of from about 5 to 40 kilodaltons.

24. (Previously presented) A pharmaceutical composition comprising the interferon-beta composition of claim 23.

this problem is not found in claims filed on 10/03/03 which were allowed

25. (Withdrawn) A method of treating a potential or developed condition or disease state in a mammalian subject with a interferon-beta 1a effective therefore, comprising administering to the subject an effective amount of an interferon-beta 1a composition comprising said interferon-beta 1a coupled to a polyethylene glycol moiety.

26. (Withdrawn) The method of claim 25, wherein the interferon-beta-1a is coupled to the polymer at a site on the interferon-beta-1a that is an N-terminal end.

27. (Withdrawn) The method of claim 25, wherein the interferon-beta-1a is coupled to the polymer at a site on the interferon-beta-1a that is at or near the C-terminal end.

28. (Withdrawn) The method of claim 25, wherein the interferon-beta-a1 is coupled to the polymer at a site by way of a glycan moiety on the interferon-beta-1a.

29. (Withdrawn) The method of claim 25, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

30. (Withdrawn) The method of claim 29, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

31. (Withdrawn) The methods of claims 25 and 29, wherein the interferon-beta-1a is a mutant interferon-beta-1a having a least one of the following properties: (a) the mutant has a higher antiviral activity than wild type interferon beta 1a, wherein the antiviral activity is measured by viral induced lysis of cells; (b) the mutant has, relative to wild type interferon-beta-1a, greater antiviral activity than antiproliferative activity; (c) the mutant binds interferon receptor but has, when compared to wild type interferon-beta-1a, lowered antiviral activity and lowered antiproliferative activity relative to its receptor binding activity.

32. (Withdrawn) A method of prolonging the activity of interferon-beta-1a in an in vivo or in vitro system, comprising coupling said interferon-beta-1a to a non-naturally-occurring polymer moiety to yield a coupled polymer-interferon-beta 1a composition, and introducing the coupled polymer-interferon-beta composition to the in vivo or in vitro system.

33. (Withdrawn) The method of claim 32, wherein the interferon-beta-1a is coupled to the polymer at a site on the interferon-beta-1a that is an N-terminal end.

34. (Withdrawn) The method of claim 32, wherein the interferon-beta-1a is coupled to the polymer at a site on the interferon-beta-1a that is at or near C-terminal end.

35. (Withdrawn) The method of claim 32, wherein the interferon-beta-1a is coupled to the polymer at a site by way of glyan moiety on the interferon-beta-1a.

36. (Withdrawn) The method of claim 32, wherein in the interferon-beta-1a is an interferon-beta-1a fusion protein.

37. (Withdrawn) The method of claim 36, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

38. (Withdrawn) The method of claims 32 and 36, wherein the interferon-beta-1a is a mutant interferon-beta-1a having at least one of the following properties: (a) the mutant has a higher antiviral activity than wild type interferon beta 1a, wherein the antiviral activity is measured by viral induced lysis of cells; (b) the mutant has, relative to wild type interferon-beta-1a, greater antiviral activity than antiproliferative activity; (c) the mutant binds interferon receptor but has, when compared to wild type interferon-beta-1a, lowered antiviral activity and lowered antiproliferative activity to its receptor binding activity.

39. (Withdrawn) The method of claim 32, wherein the polymer comprises a polyalkylene glycol.

40. (Withdrawn) The method of inhibiting angiogenesis in a subject, comprising administering to a subject an effective amount of the composition of claim 23.

41. (Previously presented) The composition of claim 7, wherein the glycosylated interferon-beta-1a comprising the amino acid sequence set forth in SEQ ID NO: 26 is an interferon-beta-1a fusion protein.

42. (Previously presented) The composition of claim 41, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

43. (**Currently amended**) A physiologically active interferon-beta composition comprising a physiologically active interferon-beta-1a comprising the amino acid sequence of SEQ ID NO: 26, coupled to a non-naturally-occurring polymer at the N-terminus of said glycosylated interferon-beta-1a, said polymer comprising a polyalkylene glycol moiety wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has an activity at least 2-fold greater relative to physiologically active interferon-beta-1b, when measured by an antiviral assay.

44. (Previously presented) The composition of claim 43, wherein the interferon-beta-1a is an interferon-beta-1a fusion protein.

45. (Previously presented) The composition of claim 44, wherein the interferon-beta-1a fusion protein comprises a portion of an immunoglobulin molecule.

46. **(Currently amended)** A physiologically active interferon-beta composition comprising a physiologically active glycosylated interferon-beta-1a, comprising the amino acid sequence of SEQ ID NO: ~~25~~ 26, N-terminally coupled to a polymer comprising a polyalkylene glycol moiety, wherein the physiologically active interferon-beta-1a and the polyalkylene glycol moiety are arranged such that the physiologically active interferon-beta-1a in the physiologically active interferon-beta composition has equal activity relative to physiologically active interferon-beta lacking said moiety, when measured by an antiviral assay.

47. (Previously presented) The composition of claim 16, wherein the interferon-beta-1a is an interferon beta fusion protein.

48. (Previously presented) The composition of claim 47, wherein the interferon beta fusion protein comprises a portion of an immunoglobulin molecule.